APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER ISSUE 1/2014

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DRUG DELIVERY EVENTS

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Provided by Christoph Blümer

Poorly Soluble Drugs Workshop (Univ. Lille Nord de France)
July 2, 2014, Lille, France — Details

International Society of Biomedical Polymers and Polymeric Biomaterials (ISBPPB): 1st Annual Conference & Exposition
July 9-12, 2014, Washington, D.C. — Details

The 41st Annual Meeting & Exposition of the Controlled Release Society
July 13-16, 2014, Chicago, IL, USA — Details

Skin Forum 14th Annual Meeting (APV 6557)
September 04-05, 2014, Prague, Czech Republic — Details

Suggest a meeting to be announced!

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosenmayr-Templeton

BREAKYL™ (MEDA)

The product was launched by MEDA under license of BDSI (BioDelivery Sciences International, Inc.) in most European countries during the year 2013. BREAKYL is commercialized in the U.S. as ONSOLIS (fentanyl buccal soluble film) by Meda's U.S. affiliate, Meda Pharmaceuticals. Breakyl is indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Each buccal film is individually sealed in a child resistant sachet, dosed with 200ug fentanyl on an area size of 0.78 cm2, 400 ug/1.56cm2, 600ug/ 2.34 cm2, 800 ug/3,11 cm2 and 1200 ug fentanyl on 4,67 cm2.

Application

The patient should with dry hands, take the Breakyl buccal film between forefinger and thumb with the pink side facing to the thumb; and place the Breakyl buccal film inside his/ her mouth, so that the pink (buccal application) side makes smooth contact with the inner lining of his/ her cheek. The Breakyl buccal film will usually dissolve completely within 15 to 30 minutes after application.

Pharmacokinetics

In a pharmacokinetic study, following buccal application, Breakyl was rapidly absorbed and the absolute bioavailability was 71 %. The absorption pharmacokinetics of fentanyl from Breakyl is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract.

A unit dose of Breakyl, if chewed and swallowed, will likely result in lower peak concentrations and lower bioavailability than when consumed as directed."

DRUG DELIVERY PEOPLE

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Provided by Prof. Dr. Karsten Mäder

KARL KOLTER, a pharmacist, obtained his Ph.D. in pharmaceutical chemistry at the University of Mainz, Germany. He started his career in 1986 in the pharmaceutical development department of what was formerly Knoll AG, Ludwigshafen, Germany, where he was involved in the development of oral liquid drugs, parenterals, sustained release drug delivery systems and drugs produced by direct compression. Several drug formulations, such as propafenone SR, were subsequently launched successfully.

In 1993, he joined BASF AG, where he was responsible for R&D in pharmaceutical excipients, drug formulations and the application technology of vitamins and carotenoids for pharmaceuticals and food.

The focus of his current work is the development of innovative excipients, mainly for solid oral dosage forms. This work has already resulted in a number of new products principally in the Kollicoat® and Kollidon® ranges, e.g. Kollicoat® IR, Kollicoat® Smartseal 30D, Kollidon® SR, Ludiflash® and Soluplus®.

In 2010, he was honored with the Award for Industry Research in Excipient Technology and in the same year one of his latest developments - Soluplus® - received the CPhI Silver Innovation Award. Karl Kolter has published more than 140 articles and posters and is inventor of more than 90 patents.

FEATURED ARTICLE

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A Brief Introduction to Biorelevant Media

By Mathew Leigh

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Summary

Biorelevant media closely resemble digestive fluids in the gastric and intestinal tracts of humans. They are used for in vitro solubility and dissolution studies of poorly soluble drugs and potentially predicting in vivo performance. This article gives an overview on biorelevant media for evaluating solubility and dissolution; towards improving drug, dosage form and formulation development of poorly water soluble drugs.

Background

Biorelevant media were first proposed [1] (Galia et al., 1998) to study solubility and dissolution of poorly soluble drugs in laboratory experiments (in vitro) rather than carry out actual animal and/or human (in vivo) studies. The scientific concept is to make fluids that closely match the composition of fluids found in the different region of the intestines. In particular, the ability of the biorelevant media to dissolve drugs to a similar extent to actual fluids is achieved by adding natural surfactants in the proportions found in human intestinal fluids.

To realize the benefits of biorelevant media for laboratory (in vitro) solubility and dissolution work, it helps to understand the composition of human intestinal fluids and their physiological response to food intake. There are two main states in the gastro intestinal tract i.e. without food and when food is ingested.

What are biorelevant media?

Biorelevant media contain chiefly bile acid salts and phospholipids (lecithin) which are natural surfactants present in human intestinal fluids. Further, pH, buffer capacity, salt content and osmolarity are similar to human intestinal fluids.

Without food, the healthy stomach juices have a pH of 1.4. This unbuffered juice contains a very small amount of surfactants and salts, likely due to reflux of upper small intestinal contents into the empty stomach.

Even without food in the small intestines, human intestinal fluids contain the natural surfactants bile acid salts and lecithins, pH averaging 6.5 and a buffer capacity of about 10 mEq/L/pH. Bile acid salts and lecithins form the colloidal structures mixed micelles. Mixed micelles in the intestinal fluid help dissolve lipophilic components (solubilization) in the diet, such as nutrients and fat soluble vitamins, thus preparing them for absorption. This solubilization process also applies to drugs that are do not fully dissolve in water. After food is eaten, not only does the composition of intestinal fluid change, but also the food becomes a constituent and greatly modifies physical and physiological properties. In the first instance, food increases the pH of the stomach depending on the type of food, typically rising to between pH 5 and 6. There are physiological changes in small intestinal fluids due to the formation of partially digested products particularly after a fatty meal. Breakdown of triglycerides, for example monoglycerides can significantly increase solubility of lipophilic drugs.

Before biorelevant media were introduced, Pharmacopeial media such as Simulated Gastric Media and Simulated Intestinal Fluid USP or buffers containing synthetic surfactants e.g. sodium lauryl sulphate were routinely used in research and development for testing solubility and dissolution profiles of poorly soluble drugs. The big limitation with these types of dissolution media is that they are mainly pH adjusted buffer solutions or essentially lack the key physiological surfactants present in human intestinal fluids, namely natural bile acid salts and lecithin. Therefore, in vitro solubility and dissolution results obtained in these media without mixed micelles would not be expected to correlate or predictive of in vivo performance for water insoluble drugs without the media being individually fine tuned. Therefore, there are sound reasons for testing in vitro drug solubility and dissolution in biorelevant media with a view towards obtaining closer in vitro-in vivo correlation for drugs that are not fully soluble in water.

Types

There are specific biorelevant media for mimicking stomach, intestines and colonic fluids.

Biorelevant media mimicking digestive fluids in the fasted state gastric fluid are known as Fasted State Simulated Gastric Fluid [2] (Vertzoni et al, 2005) (FaSSGF) whilst the fed state media are called Fed State Simulated Gastric Fluid (FeSSGF) (Jantratrid and Dressman, 2009). Biorelevant media mimicking digestive fluids in the fasted state upper small intestine are known as Fasted State Simulated Intestinal Fluid (FaSSIF) whilst the fed state media are called Fed State Simulated Intestinal Fluid (FeSSIF) (Galia et al, 1998).

In general, simulating the fluid found in the upper small intestine is most common and important because it is from this fluid in vivo that most poorly soluble drugs are dissolved before being absorbed.

There are currently two types of fasted state biorelevant media composed of bile acid salts and lecithin for simulating human intestinal fluid and assessing in vitro drug solubility and dissolution, known by the acronyms FaSSIF and FaSSIF-V2 [3] (Jantratrid and Dressman, 2009).

The main variations in the two media are the mole ratio of bile salt to lecithin and buffers used for producing biorelevant media with pH 6.5 matching human intestinal fluid. FaSSIF uses a phosphate buffer and FaSSIF-V2 a maleate buffer. The mole ratio of bile salt to lecithin in the original and earlier version of fasted state intestinal fluid (FaSSIF) is 4:1. The ratio for a later version (FaSSIF-V2) is 15:1. These two ratios are within the physiological range in human intestinal fluids. Fasted state media (FaSSIF and FaSSIF-V2) are more frequently used to benchmark in vitro solubility and dissolution [4] (Leigh et al, 2013) of poorly soluble drugs (compared to fed state media) due to the fact that they mimic the composition of human intestinal fluids in the fasted state upper small intestine. The composition of human intestinal fluids in the fasted state is less variable since there is little interference from ingested food.

How can biorelevant media help you during drug development?

Because biorelevant media mimic upper small intestinal fluids, they can provide a better indication of how drugs are likely to dissolve and release from their formulations in vivo based on in vitro solubility tests and dissolution tests respectively. The media may be used for both immediate and controlled release formulations. Biorelevant media are an extremely useful tool during R&D of new drugs and existing generic drugs from Class 2 and Class 4 compounds that are insoluble in water. The dissolution data generated using biorelevant media can support dosage form as well as formulation changes made to the drug product.

Discovery

In discovery, the primary use of biorelevant media is to find out if the new drug is likely to have very low in vivo solubility. This can be tested using the traditional shake flask method and help identify if the solubility is sufficient or a special formulation approach is likely to be required. Permeability studies e.g. Caco2 cells [5](Frank et al, 2012) can also be carried out in FaSSIF to evaluate drug permeability under fasted state conditions.

Pre-clinical

In pre-clinical, the media can be used to compare multiple formulations of poorly soluble drugs. Such studies can be carried out using conventional laboratory equipment such as standard Pharmacopeial dissolution equipment. If the amount of drug or its formulation is in short supply, miniaturized dissolution equipment [6] may be used.

Clinical

In clinical formulation development, the media can be used in combination with modeling software as part of obtaining in vivo-in vitro correlation (IVIVC). This can be useful if there are formulation changes for a given drug or to increase the chances of successfully developing a bioequivalent formulation that is the same as the original reference standard. Large numbers of animal studies and even human may be avoided by establishing correlation between in vitro dissolution of the dosage form with its in vivo performance.

Future prospects

The use and integration of biorelevant media into the development tool kit will continue to support the selection of drugs (and their formulations) with superior physicochemical properties. Standardized protocols for testing of different drugs in specific biorelevant media are being researched and developed as part of an IMI (Innovative Medicines Initiative) Project: ORBITO Innovative Tools for Biopharmaceutics. Further, coupling of biorelevant media with in silico modeling software will continue to facilitate the selection and development of superior drugs and their dosage forms for increasing numbers of insoluble drugs with reduced dependency on animal studies.

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DRUG DELIVERY LITERATURE

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Provided by Dr. Carsten Timpe

RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

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ABOUT THE FOCUS GROUP

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The APV Drug Delivery Focus Group (APV DD) is a section of the APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. / International Association for Pharmaceutical Technology), a major European society for those sharing a professional interest in pharmaceutical sciences. The Focus Group was established in 2003 in response to the increasing importance of drug delivery within modern pharmaceutics.

Read more. ***Contact us.***

COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

OUR MISSION STATEMENT:

Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

Our mission includes in particular the following tasks:

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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